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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,069	08/24/2006	Peter Mayrhofer	Q90909	6079

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
06/10/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/556,069	MAYRHOFER ET AL.
	Examiner	Art Unit
	SUMESH KAUSHAL	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8 and 10-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8 and 10-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 03/15/11 has been acknowledged and fully considered.

Claims 1-3, 5-8 and 10-32 are pending and are examined in this office action.

Election/Restrictions

Applicant's election without traverse of *ParA Resolvase* in the reply filed on 03/15/11 is acknowledged.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

The instant specification fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures because: *The specification fail to provide SEQ ID NO(s) for the nucleotide sequences disclosed on pages 17-18 and 20-21.*

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-8, 10-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention

The instant invention relates to plasmid expression vector, which is capable of dividing into a miniplasmid and a minicircle upon the expression of a sequence specific recombinase (ParA) and isolation of minicircles.

Breadth of Claims and Guidance Provided by the Inventor

The scope of instant claims encompasses a plasmid comprising a prokaryotic origin of replication, a marker sequence, two specific recombinase recognition sequences and a multiple cloning site that comprises a gene coding for a sequence specific recombinase, whereby the units are arranged on the plasmid in such a way that the plasmid is divided into a miniplasmid and a minicircle upon expression of the sequence specific recombinase, wherein the miniplasmid comprising the prokaryotic origin of replication, the marker sequence and the gene for the sequence specific recombinase and said minicircle comprising the multiple cloning site. In addition the scope of invention as claimed further encompasses a minicircle derived from the plasmid (as claimed) wherein the minicircle is attached to a becterial ghost over any hydrophobic membrane anchoring peptide. In addition the scope of the invention as claimed further encompasses a kit and method producing therapeutically useful minicircles by transfecting the plasmid (as claimed) and culturing bacteria during which the recombinase is express to produce miniplasmids and minicircles.

At best the specification as filed teaches plasmid(s) which upon the conditional expression of ParA recombinase (induced via arabinose) results in **miniplasmid** comprising i) origin of replication and ii) a marker gene (drug resistance gene) whereas

the **minicircle** comprises i) gene encoding ParA resolavse operavbly linked to araC repressor/inducer, ii) identification sequence (lac operator) and ii) an anchoring peptide (lacI-L fusion protein) see Figure 5; and Spec. Pages 22-25). The speciation as filed fails to disclose any other plasmid structure which would enable one skilled in the art to practice the invention as claimed (see claim 1) in a predictable fashion without further undue amount of experimentation. The specification fails to disclose any plasmid vector which comprises "*functional units arranged in such a way that the plasmid is divided into a miniplasmid and a minicircle upon expression of the sequence specific recombinase (Para resolvase), said miniplasmid comprising the prokaryotic origin of replication, the marker sequence and the gene for the sequence specific recombinase and said minicircle comprising the multiple cloning site*".

Furthermore, regarding the minicircle identification sequence used for the identification and isolation of the minicircles, besides lacO that binds to lacI-L (hybrid fusion anchoring peptide: LacI+MS2L), the specification fails to disclose any other identification/isolation system, which would enable one skilled din the art to practice the invention as claimed (see claim 5-8, 27-32) in a predictable fashion without further undue amount of experimentation.

In addition, besides inducing bacterial lysis for isolation of minicircles by co-transfecting another plasmid (E-specific/temperature-specific bacterial lysis), the specification as filed fails to disclose any other bacterial lysis system(inducible), which would enable one skilled in the art to practice the invention as claimed (see claim 21-22, 27-32) in a predictable fashion without further undue amount of experimentation.

State of Art, Predictability and Quantity of Experimentation Required

State of the art at the time of filing was such that the DNA as an active agent is among the most promising technologies for vaccination and gene therapy. However, plasmid backbone sequences needed for the production of plasmid DNA in bacteria are dispensable, reduce the efficiency of the DNA agent and, most importantly, represent a biological safety risk. Conventional plasmid DNA can be subdivided into a bacterial backbone and a transcription unit. The transcription unit usually carries the target gene

or sequence along with necessary regulatory elements. The bacterial backbone includes elements like antibiotic resistance genes, an origin of replication, undermethylated CpG motives and potentially cryptic expression signals. Some of these sequences are required for the production of plasmid DNA, but each of them represents a serious biological safety problem which can lead to adverse side effects if it is administered to patients. Thus regulatory agencies recommended totally avoiding the use of antibiotic resistance genes. Much effort has been made to overcome these biosafety problems using minicircle DNA for non-viral gene transfer containing only the therapeutic useful transcription units. Furthermore, it has been shown that minicircles can be produced in vivo using variety of recombinases like parA resolvase. These enzymes recognize the corresponding recombination sites and excise DNA sequences located between them. If the origin of replication and the antibiotic resistance gene are flanked by the recognition sequences, the recombinase divides the original plasmid into (i) a replicative miniplasmid carrying these undesired sequences, and (ii) a minicircle carrying only the therapeutic expression unit (See Jechlinger et al J Mol Microbiol Biotechnol. 8(4):222-31, 2004, Mayrhofer et al, J Gene Med. 10(11):1253-69, 2008) Thus the plasmid design that recombines to produce desired miniplasmid and minicircles is considered germane to the success of instant invention. As stated earlier the specification as filed fails to disclose any plasmid vector which comprises "functional units arranged in such a way that the plasmid is divided into a miniplasmid and a minicircle upon expression of the sequence specific recombinase (Para resolvase), said miniplasmid comprising the prokaryotic origin of replication, the marker sequence and the gene for the sequence specific recombinase and said minicircle comprising the multiple cloning site".

Furthermore an essential requirement for an efficient recombination system is the stringent repression of the recombinase prior to expression. If the recombinase is not efficiently repressed prior to induction, miniplasmids will accumulate thereby displacing the origin plasmid. For example if the parA resolvase gene is cloned under expression control of the araB promoter along with lysis plasmid pKLys36.1, the plasmid will have a

lower copy number compared to the plasmid carrying the resolution sites leading to lower recombination efficiency indicating that a high ratio of ParA resolvase to plasmid is necessary to achieve close to 100% recombination. Similarly considering the scope of instant invention it is not clear whether the inducible lysis gene is express from a single plasmid or co-transfected separately (see claim 21). Thus the invention as broadly claimed in the instant application would not result in the production of desired products (miniplamids and minicircles), since the stringent control of repression and expression of the site-specific recombinase in E.coli is of high importance. In the first place, the expression system should efficiently silence gene expression prior to induction to avoid premature recombination leading to the displacement of the parental plasmid by the miniplasmid. The invention as broadly claimed herein does not require the stringent control of repression and expression of the site-specific recombinase and lysis gene.

In addition, the invention as claimed requires a mincicircle identification sequence that specifically binds to a hydophobic membrane anchoring peptide. Therefore stringent control of repression and expression of the anchoring peptide or its modification (to make hydrophobic anchoring) is of high importance as the anchoring peptide would easily impair the DNA replication and or DNA binding functionalities (required for micnicircle isolation or formation of bacterial gosts).

The state of the art clearly suggests that the development of a system that provides efficient production of minicircles consisting of origin or replication and therapeutic gene alone (see Mayrhofer et al, J Gene Med. 10(11):1253-69, 2008) would overcomes the more than 10-year-old problem of inefficient recombination that leads to: (i) low product yield and (ii) the lack of an appropriate minicircle-DNA purification technique. Lack of product homogeneity caused by multimeric forms of the recombination products as well as mixed concatemers has also been an issue hampering pharmaceutical applications. The high recombination yields achieved in a scalable fermentation process combined with the high performance affinity chromatography technique of the RBPS-Technology defines a novel state of the art minicircle-DNA production.

Furthermore, It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In the instant case it is not clear how one would generate the minicircles (as claimed), using the plasmid (as claimed), wherein the functional units are arranged in such a way that plasmid divides into minicircle and miniplasmids (as claimed).

At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case combinations required to design the plasmid (as claimed) are unlimited and would not lead to predictable results without extensive and undue amount of experimentation. The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973).

In instant case making plasmid vectors having variety of functional units arranged in such a way that the plasmid is divided into a miniplasmid and a minicircle upon expression of the sequence specific recombinase, wherein the miniplasmid comprising the prokaryotic origin of replication, the marker sequence and the gene for the sequence specific recombinase and said minicircle comprising the multiple cloning site is not considered routine in the art and without sufficient guidance to a specific arrangement of individual functional units in context of repression/expression of desired units, the experimentation left to those skilled in the art is unnecessarily, and improperly,

extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUMESH KAUSHAL whose telephone number is (571)272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sumesh Kaushal/
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